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1634

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ELECTRONIC

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DETAILED ACTION

1. This action is in response to the amendment filed April 6, 2011. Applicant's remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicant's amendments. Any rejections or objections not reiterated herein have been withdrawn. This action is made FINAL.

Claims 5-25, 28-30, 32-34, 36, 56-58, 62, 67-72, 75-76, and 79-83 are currently pending.

Claims 9-25, 28-30, 32-34, 36, 56-58, 62, 67-72, 75-76, and 79-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 24, 2009.

Response to Declarations

2. The declaration under 37 CFR 1.132 filed on April 6, 2011 is insufficient to overcome the enablement rejection set forth in the last Office action. For a detailed explanation please see paragraphs 5 and 6 below.

Withdrawn Objections

3. The objection made to the abstract in section 3 of the Office Action of October 29, 2010 is withdrawn in view of the amendments made to the abstract.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a new rejection necessitated by amendment

Claims 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-8 are indefinite over the recitation of the phrase "whereby a higher gene copy number indicates the presence of a cancer or precancerous condition". This phrase is considered indefinite because it is unclear if "higher gene copy number" refers to the copy number determined in the sample from the mammal suspected of having cancer or a precancerous condition (step (a)) or if it refers to the copy number determined in a sample from a mammal of the same species not having cancer of the type being diagnosed (step (b)).

Claim Rejections - 35 USC § 112 1st paragraph

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5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified in response to the amendmendments:

Claims 5-8 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for diagnosing a predisposition to hepatocellular carcinoma in a human patient, comprising: (a) obtaining a liver tissue sample from said human suspected of having hepatocellular carcinoma (b) assaying said liver tissue sample to determine the gene copy number of HSPC150; (c) diagnosing said human patient with a predisposition to hepatocellular carcinoma when the gene copy number of HSPC150 is increased in said liver tissue sample relative to the gene copy number of HSPC150 in a non cancerous liver tissue control sample.

does not reasonably provide enablement for a diagnostic assay for any type of cancer or precancerous condition in any type of mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Nature of the Invention

The invention is drawn to a diagnostic assay for cancer or a precancerous condition in a mammal. The method comprises (a) obtaining a cell or tissue sample from a mammal suspected of having cancer or a precancerous condition and determining for said sample the gene copy number of the HSPC150 gene (b) determining a normal HSPC150 gene copy number in a corresponding cell or tissue from a mammal of the same species no having cancer of the type being diagnosed, (c) comparing said gene copy and said normal HSPC150 gene copy number. The whereby

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clause states that a higher gene copy number indicates the presence of a cancer or precancerous condition and results in a diagnosis of cancer or a precancerous condition in said mammal. Thus the nature of the invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of any cancer or any precancerous condition in any type of mammal. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (*Mycolgen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Scope of the Claims:

The claims are drawn to a diagnostic assay for cancer or a precancerous condition in a mammal. The claims broadly encompass a diagnostic assay for any type of cancer (breast, colon, cervical, lung, brain etc) or any type of precancerous condition (actinic keratosis, atrophic gastritis, cervical dysplasia etc). Only claim 7 is limited to specific cancers wherein the cancer is selected from the group consisting of breast, colon, lung, prostate, ovarian, pancreatic, cervical, and kidney cancer. Additionally the claims broadly encompass a diagnostic assay for any type of mammal (human, cat, whale, bat). Only claim 6 is limited to a specific type of mammal wherein the mammal is a human. Further the claims encompass obtaining a cell or tissue sample wherein the cell or tissue is derived from anywhere (i.e., saliva, hair, breast tissue).

Teachings in the Specification:

The specification teaches that the present invention relates to genes that have been identified as being amplified and/or over expressed, which can include increased

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copy number thereof, in cancerous cells. The genes have been identified through a combination of CGH, SKY, expression analysis, and reverse transcriptase PCR. The genes are listed in Table 1.

In the instant case the elected gene, HSPC150 protein similar to ubiquitin-conjugating enzyme, is listed in Table 1. Specifically Table provides the following information about HSPC150-- serial no: 119, SEQ ID NO: 107, Accession no: AI990409, tissue: breast, p_m: metastatic, chromosome: 1, band: q32.1, unigene: Hs.5199. As stated in the declarations under 37 CFR 1.132 filed on April 6, 2011, the genes listed in Table 1 are both over expressed and show an increased copy number.

The declarations however do not overcome the enablement rejection for several reasons. For example Table 1 teaches that the tissue is breast. Here its unknown if this means that the HSPC150 gene was only associated with breast cancer (opposed to the other types of cancers and pre cancerous conditions encompassed by the claims) or if this means that the HSPC150 gene was only detected in breast tissue samples (opposed to being detected in other types of samples encompassed by the claims). Further its unclear if the genes that were identified as being amplified or over expressed, were detected in a representative number of different types of mammals since the claims encompass any mammal.

State of the Art and the Unpredictability of the Art:

The prior art Crawley (Genome Biology 2002 Vol 3 No 12) identified frequent cytogenic aberrations in hepatocellular carcinoma (abstract). Crawley teaches that

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although techniques such as comparative genomic hybridization have traditionally been used to identify cytogenetic aberrations, it might also be possible to identify them indirectly from gene expression studies. Crawley teaches a list of genes whose expression changed at least twofold in 70% of tumor samples in the same relative direction as the cytogenic change and are located in regions identified as cytogenetically abnormal by CGMA in at least 35% of samples (Table 2). Relevant to the instant claims the HSPC150 gene is listed in Table 2 of Crawley. There was a 5.6 fold difference in tumor tissue gene expression relative to non cancerous tissue for the HSPC150 gene located at 1q:209. Crawley teaches that gene expression profiling data is able to predict cytogenetic changes that frequently occur in HCC (page 6). As such the prior art of Crawley provides support for a reliable association between an increased copy number of the HSPC150 gene and the presence of hepatocellular carcinoma in human patients.

Even though there is evidence in the prior art that the HSPC150 gene has an increased copy number in hepatocellular carcinoma it is highly unpredictable as to whether the results obtained with hepatocellular carcinoma could be extrapolated to other cancers and pre cancerous conditions. For example Adnane (Oncogene 1991 Vol 6 pages 659-663) teaches that the analysis of 387 human breast tumor DNAs revealed that BEK (also called FGFR2) was amplified in about 12% of the cases (page 659, col 2). On the other hand Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) teaches a genome microarray spotted with 287 target genes was used to analyze resected tissue from 11 different high grade gliomas. A high frequency of deleted

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genes was observed in 6 of 11 cases (54.5%), including FGFR2 (abstract). These papers are relevant to the present situation because they support the argument that it is highly unpredictable as to whether the amplification of HSPC150 in hepatocellular carcinoma could be extrapolated to other cancers and precancerous conditions.

Further even though there is evidence in the prior art that the HSPC150 gene has an increased copy number in humans with hepatocellular carcinoma it is highly unpredictable as to whether the results obtained with humans could be extrapolated to other mammals. Knowledge that a particular gene such as HSPC150 is amplified in one organism (i.e. humans) with hepatocellular carcinoma does not allow one to conclude that this gene will also be amplified in other organisms with hepatocellular carcinoma.

Quantity of Experimentation:

In the instant case there is no evidence in the specification that increased copy number of HSPC150 is actually associated with a representative number of different cancer or precancerous conditions. For this reason one would have to conduct extensive experimentation. For example, such experimentation may involve using probes specific for HSPC150 gene to detect the copy number of the HSPC150 gene in large number of samples obtained from all different types of mammals with all different types of cancer and precancerous conditions. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

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Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response To Arguments Regarding Enablement

6. In the response (page 11) the Applicants state that a diagnostic assay is known to be an assay that can be used to help diagnose a condition. The Applicants state that final diagnosis is generally determined after evaluating the results of several screening assays. They argue that according to the MPEP, “to enable a diagnostic assay use, a disclosure merely needs to teach how to make and use the assay for screening purposes”.

This argument has been fully considered. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the specification coupled with information known in the art without undue experimentation. The “whereby” clause of claim 5 states that a higher gene copy number (of HSPC150) indicates the presence of a cancer or precancerous condition and results in a diagnosis of cancer or a precancerous condition. The claims broadly encompass the genus of any cancer or any precancerous condition. In applications directed to inventions in art where the results are unpredictable, the disclosure of a single species (here the species is breast cancer), does not provide adequate basis to support generic claims drawn to any

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cancer or precancerous condition. Proof of enablement is required for other members of the claimed genus of any cancer or precancerous condition because the Examiner has established that it is highly unpredictable as to whether the results obtained with one cancer could be extrapolated to other cancers and pre cancerous conditions. For example, the prior art of Adnane (Oncogene 1991 Vol 6 pages 659-663) teaches that BEK (also called FGFR2) is amplified breast cancer, while the prior art of Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) teaches that FGFR2 is deleted in gliomas. Therefore a person skilled in the art can not use the diagnostic assay for any cancer or precancerous condition without undue experimentation.

In the response (page 11), the Applicants state that the present invention is not in the class of inventions characterized as the unpredictable arts.

This argument has been fully considered but is not persuasive. The nature of the invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of any cancer or any precancerous condition in any type of mammal. The invention is considered to be in a class of inventions that is unpredictable because it is not obvious from the disclosure of one species (breast cancer) that other species will work.

In the response (pages 11-12) the Applicants argue that a diagnostic assay merely assists in a diagnosis and that all diagnostic assays are subject to some level of false results. Applicants state that they do not know what is meant by a "reliable" association. They state that as an example of the relationship they have shown that the subject gene HSPC150 is related to breast cancer. They further note that true utility of

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any given biotechnology innovation is determined by the FDA and related regulatory organizations, and eventually by the marketplace.

This argument has been fully considered. The examiner agrees that there is no requirement for a diagnostic assay to be 100% reliable; however some degree of reliability is required. Because the teachings in the specification are limited to breast cancer, the specification does not teach a reliable association between an increased copy number of the HSPC150 gene and any other type of cancer or precancerous conditions. As stated above, the disclosure of a single species (breast cancer) does not provide an adequate basis to support any type of cancer and any precancerous condition. Further it is noted that considerations made by the FDA are different from those made the Office in determining whether a claim is enabled.

In the response (page 12) the Applicants argue that it is not relevant that the claims encompass a method wherein (i) the cancer or precancerous condition is any type of cancer or precancerous condition (ii) the mammal is any type of mammal, and (iii) the cell or tissue is derived from anywhere. They state that any tissue can be tested. They state that any mammal can be tested. They assert that there is no undue experimentation by the user because the user simply runs the test and makes a decision using this test in conjunction with other knowledge or tests.

This argument has been fully considered but is not persuasive. The breadth of the claims is one of several factors that are considered when determining whether a disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. Because the claims encompass the genus of any type of

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cancer or precancerous condition it is relevant to note that it is unpredictable as to whether it is possible to extrapolate the finding that the HSPC150 gene has an increased copy number in one type of cancer to other types of cancers and precancerous conditions. The examiner has even cited two references to support this argument (Adnane and Sasaki). Because there is no evidence in the specification that increased copy number of HSPC150 is associated with a representative number of different cancer or precancerous conditions, additional experimentation is required. One would have to perform extensive experimentation using probes specific for HSPC150 gene to detect the copy number of the HSPC150 gene in large number of samples obtained from mammals with all different types of cancer and precancerous conditions. Additionally, it is noted that knowledge that HSPC150 is amplified in humans with cancer does not allow one to conclude that this gene will also be amplified in non human mammals with cancer. Therefore additional experimentation would be needed to establish that increased copy number of HSPC150 is indicative of cancer or a precancerous condition in a representative number of different mammals. Finally it is noted that one of skill in the art would appreciate that the sample source is relevant because for example, you can not detect brain cancer by determining the copy number of a particular gene in an ovarian tissue sample. It is well known in the art that gene expression and copy number patterns vary and are characteristic for a given cell type.

In the response (pages 12-13) the Applicants argue that Table 1 is a list of genes identified in cancerous cells as being both over expressed and showing increased copy number. They direct the Examiners attention to the declarations filed under 35 USC

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1.132.

This argument and the declarations have been fully considered. The Examiner has been persuaded that the genes listed in Table 1 are both over expressed and show an increased copy number in cancerous cells. However the Applicants have not met the burden of adequately describing the data in the specification. For example Table 1 teaches that the tissue is breast. Here its unknown if this means that the HSPC150 gene was only associated with breast cancer (opposed to the other types of cancers and pre-cancerous conditions encompassed by the claims) or if this means that the HSPC150 gene was only detected in breast tissue samples (opposed to being detected in other types of samples encompassed by the claims). Further it's unclear if the genes that were identified as being amplified or over expressed, were detected in a representative number of different types of mammals since the claims encompass any mammal.

In the response (page 14) the Applicants argue that working examples are not required by the statute, rules, or the case law. They state that the claims are directed to a diagnostic test. They state that the level of skill in the art is known to be high and the level of enablement required for a diagnostic test is low. They assert that the specification has provided considerable direction and guidance on how to practice the claimed invention, particularly given the high level of skill in the art.

This argument has been fully considered but is not persuasive. When considering the factors related to a determination of non enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself

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render the invention non enabled. Further it is noted that the level of enablement required for a diagnostic test is not low, particularly when the test requires the analysis of genetic information. While the level of skill in the art is deemed to be high, the unpredictability with regard to correlating the copy number of a particular gene with a particular phenotype is even higher. For these reasons the enablement rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection has been modified in response to the amendments:

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8. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crawley (Genome Biology 2002 Vol 3 No 12 pages 1-8 published online 11/25/2002).

Regarding Claim 5 Crawley teaches obtaining liver samples from human patients with hepatocellular carcinoma (HCC) and corresponding non cancerous liver samples. Crawley teaches determining the level of HSPC150 gene expression in the samples. Crawley teaches that HSPC150 gene had a 5.6 fold difference in tumor tissue gene expression relative to non cancerous tissue (abstract, page 7, col 1-2, and Table 2). As such Crawley teaches a method comprising: obtaining a cancerous liver sample from a human and determining the level of HSPC150 RNA in the sample, determining the level of HSPC150 RNA in a non cancerous liver sample, and comparing the level of HSPC150 RNA in the cancerous liver sample to the level of HSPC150 RNA in the non-cancerous liver sample.

Regarding Claim 6 Crawley teaches a method wherein the samples were obtained from a human (page 7, col 1).

Crawley does not teach directly determining the gene copy number of the HSPC150 gene in a sample from a human suspected of having HCC and non-cancerous liver samples. Further Crawley does not teach comparing the gene copy numbers.

However Crawley teaches that using comparative genomic microarray analysis (CGMA) it is possible to predict chromosomal amplifications and deletions by organizing gene expression data by genomic mapping location and scanning for regions that contain a statistically significant number of gene expression values that change in the

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same relative direction (abstract, page 2, col 1). Crawley teaches that they applied CGMA analysis to a large HCC microarray dataset to demonstrate its validity as an alternative to CGH and to identify candidate genes in regions of frequent cytogenic change. Crawley teaches that using CGMA they identified 13 regions of cytogenic change in the HCC samples, including +1q which is the region where the HSPC150 gene is located. (abstract, page 2 col 2, and Table 2). As such Crawley predicts that the HSPC150 gene is amplified (i.e. has an increased copy number) in HCC samples relative to non-cancerous samples.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Crawley by detecting the copy number of the HSPC150 gene in a sample obtained from a human suspected of having HCC. Crawley teaches that although techniques such as comparative genomic hybridization have traditionally been used to identify cytogenic aberrations, it might also be possible to identify them indirectly from gene expression studies. Crawley teaches CGMA predicts regions of cytogenic change by searching for regional gene expression biases. Based on the teachings in Crawley one of skill in the art would have been motivated to detect the copy number of the HSPC150 gene in the samples using a technique such as CGH in order to confirm the results found using the CGMA assay and to determine if CGMA is an accurate predictor of chromosomal imbalance. Because Crawley predicts that the HSPC150 gene is amplified (i.e. has an increased copy number) in HCC samples relative to non-cancerous samples a method for diagnosing hepatocellular cancer by detecting an increased copy number of HSPC150 relative to

non cancerous cells would have been obvious to one of skill in the art at the time of the invention.

The following rejection has been modified in response to the amendments:

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Crawley (Genome Biology 2002 Vol 3 No 12 pages 1-8 published online 11/25/2002) in view of GenBank (Accession No AI990409 GI 5837290 entered 9/7/1999).

Regarding Claim 8 Crawley does not teach a method wherein the HSPC150 gene encodes the same gene product as the polynucleotide of SEQ ID NO: 107.

However GenBank teaches a nucleic acid sequence that is 100% identical to SEQ ID NO 107. (QY=SEQ ID NO: 1, Db=GenBank sequence).

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QY      1 CAACATTAAATGACTATTTATTTTTCAGGTTTAAAAGATTTCAAAATACATATGTACAAG 60
      |||
Db      1 CAACATTAAATGACTATTTATTTTTCAGGTTTAAAAGATTTCAAAATACATATGTACAAG 60

QY      61 ATAAATAAACTACACAAAATTATGTCATCAAAATATTTAAAAAAAATTCAAGGTAGG 120
      |||
Db      61 ATAAATAAACTACACAAAATTATGTCATCAAAATATTTAAAAAAAATTCAAGGTAGG 120

QY      121 CAACTTAGATCACCTTGGCAAAGAACACATTAAGTGAACAGGACAAGTCCCTTA 180
      |||
Db      121 CAACTTAGATCACCTTGGCAAAGAACACATTAAGTGAACAGGACAAGTCCCTTA 180

QY      181 AACATCAGGATGAAATTTCTTTCTATGCCTACTAGCTGACTGGCCTTCCTTTCTGTGT 240
      |||
Db      181 AACATCAGGATGAAATTTCTTTCTATGCCTACTAGCTGACTGGCCTTCCTTTCTGTGT 240

QY      241 TGAGTTGTGTACTCTGGAGTCACCAAGCCTCTGGTAGATTATCAAGCATCTCTTCCTCATC 300
      |||
Db      241 TGAGTTGTGTACTCTGGAGTCACCAAGCCTCTGGTAGATTATCAAGCATCTCTTCCTCATC 300

QY      301 AGCCTTTTGTTTCTGTCTTGCATGCTTCTGTGCCACTGTCTGGCATTCTTGAGGAAGGC 360
      |||
Db      301 AGCCTTTTGTTTCTGTCTTGCATGCTTCTGTGCCACTGTCTGGCATTCTTGAGGAAGGC 360

QY      361 TGGCTTATTATATTTAAATTCTGAGGATATGTCAGCCATGAGCGGGTCATCAGGGTTGGG 420
      |||
Db      361 TGGCTTATTATATTTAAATTCTGAGGATATGTCAGCCATGAGCGGGTCATCAGGGTTGGG 420

QY      421 TTCTGACATGAGCAGCTGAATAGAGGTCAACACAGTTGCGATGTTGAGGGATGGTCTCCA 480
      |||
Db      421 TTCTGACATGAGCAGCTGAATAGAGGTCAACACAGTTGCGATGTTGAGGGATGGTCTCCA 480

QY      481 AGCACCTTTTGGTGGCAATTTGAGAACATCCAGACAAATCCTCCAGCAGAATCAATGTN 540
      |||
Db      481 AGCACCTTTTGGTGGCAATTTGAGAACATCCAGACAAATCCTCCAGCAGAATCAATGTN 540

QY      541 TGGATGATAAATTGGAGTGAGAAATCGGATCTGAGGAGGTTCAAATGGGTACCTTTCAAG 600
      |||
Db      541 TGGATGATAAATTGGAGTGAGAAATCGGATCTGAGGAGGTTCAAATGGGTACCTTTCAAG 600

QY      601 AATGATTACTGTTAGCTTAAAAACACCCTTCTCATAAGGTGTGGTGTGCTCCAACTAATAT 660
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Db      601 AATGATTACTGTTAGCTTAAAAACACCCTTCTCATAAGGTGTGGTTGCTCCAATAATAT 660
Qy      661 TTGAGCTCGCAAGTCATCCATTGGTCTTATCTTGGCAACATGTGATGGCCGGGGGTGGT 720
        |||
Db      661 TTGAGCTCGCAAGTCATCCATTGGTCTTATCTTGGCAACATGTGATGGCCGGGGGTGGT 720
Qy      721 CTGTGGCAACATGTGCACTATCTC 744
        |||
Db      721 CTGTGGCAACATGTGCACTATCTC 744

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Since these sequences are 100% identical it is a property of the GenBank sequence that it encodes the same gene product as SEQ ID NO: 7.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Crawley by detecting the copy number of a gene that encodes the same gene product as the polynucleotide of SEQ ID NO: 107. In the instant case GenBank teaches a nucleotide sequence that is 100% identical to SEQ ID NO: 107 and therefore encodes the same gene product as SEQ ID NO: 107. Because Crawley predicts that the HSPC150 gene is amplified in HCC one of skill in the art would have been motivated to detect the copy number of the GenBank sequence that encodes the same gene product as the polynucleotide of SEQ ID NO: 107 for the benefit of being able to determine the copy number of the HSPC150 gene.

Response To Arguments- 35 USC 103

10. In the response (page 14) the Applicants state that the Examiner is being inconsistent with arguments. They state that the Examiner has argued that it is unpredictable as to whether the results obtained with hepatocellular carcinoma could be extrapolated to other cancers and pre-cancerous conditions but then cites the same reference as rendering the present invention obvious.

This argument has been fully considered but is not persuasive. The instant claims have been rejected under 35 USC 103 as being obvious in view of the prior art and have been rejected under 35 USC 112 1st paragraph as not fully enabled by the specification. In the instant case, where the prior art does render obvious particular embodiments of the broadly claimed methods, the prior art is not sufficient enable the skilled artisan to practice the claimed method in the full scope of the claims. Based on the disclosure of Crawley, a diagnostic assay for hepatocellular carcinoma in humans that comprises determining the copy number of HSPC150 would have been obvious at the time of the invention. However Crawley does not provide enablement for a diagnostic assay for any cancer or precancerous condition in a mammal that comprises determining the copy number of HSPC150.

In the response (page 15) the Applicants argue that claim 7 is directed to specific cancers, whereas Crawley is directed to hepatocellular carcinoma.

This argument has been fully considered but is irrelevant since claim 7 is not rejected under 35 USC 103 in view of Crawley.

In the response (page 15) the Applicants state that Crawley discloses use of comparative genomic microarray analysis (CGMA) to predict regions of cytogenic change by searching for regional gene expression biases. The Applicants argue that CGMA is an indirect means of identification from gene expression studies. The Applicants further summarize the teachings in Crawley.

This argument has been fully considered but is not persuasive. The instant claims encompass determining the gene copy number of a HSPC150 gene by any

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means. They are not limited to methods of directly detecting gene copy number (i.e., CGH). Crawley states that CGMA predicted frequent gains for chromosome 1q (gained in 72% of tumor samples). This is the location of the HSPC150 gene. Crawley further teaches that they compared their results to previous HCC studies and CGMA produced 10 of 13 (77%) predictions that matched a consensus chromosomal aberration profile. This suggests that CGMA profiling is able to predict regions of frequent chromosomal imbalance in HCC as well as CGH.

In the response (page 16) the Applicants argue that Crawley does not teach or suggest a diagnostic assay for cancer. They state that Crawley discloses an alternative to CGH profiling when gene expression profiling data is available. However they state that Crawley does not provide any teaching related to the use of any of the gene listed in the reference in a diagnostic assay for cancer.

This argument has been fully considered but is not persuasive. In the instant case the rejection is based on the fact that the reference renders obvious the claimed method steps. In the instant case the preamble of “a diagnostic assay for cancer or a precancerous condition in a mammal” is considered to be an intended use of the claimed method. Additionally the wherein clause which recites that a higher gene copy number indicates the presence of a cancer or precancerous condition and results in a diagnosis of cancer or a precancerous condition is broadly interpreted as a property of the copy number of HSPC150.

In the response (page 16) the Applicants argue that Crawley does not teach or suggest determining the copy number of the HSPC150 gene in suspect tissue and

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comparing it to the copy number of the HSPC150 gene in normal tissue. Further they argue that the term copy number cannot be found in the Crawley reference.

This argument has been fully considered but is not persuasive. Crawley teaches that HSPC150 gene had a 5.6 fold difference in tumor tissue gene expression relative to non cancerous tissue (abstract, page 7, col 1-2, and Table 2). Additionally Crawley states that CGMA predicted frequent gains for chromosome 1q (gained in 72% of tumor samples). This is the location of the HSPC150 gene. As such Crawley predicts that the HSPC150 gene is amplified in HCC samples relative non cancerous samples. One of skill in the art would recognize that if a gene is amplified it means that there is an abnormal number of copies of that gene. Further the claims do not require directly determining the HSPC150 copy number.

In the response (page 16) the Applicants argue that Crawley does not teach or suggest that HSPC150 amplification is indicative of cancer.

This argument has been fully considered but is not persuasive. Crawley predicts that the HSPC150 gene is amplified (i.e. has an increased copy number) in HCC samples relative non cancerous samples. Therefore a method for diagnosing hepatocellular cancer by detecting an increased copy number of HSPC150 relative to non cancerous cells would have been obvious to one of skill in the art at the time of the invention.

Conclusion

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11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda M. Shaw/
Examiner
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